NEUROLOGICAL INFECTIOUS DISEASES THERAPY IN NEUROLOGY III

Karen L. Roos, MD
Indiana University School of Medicine

Approach to the patient with fever and headache –bacterial meningitis or encephalitis with an emphasis on when to add dexamethasone to the initial antimicrobial regimen:

The clinical presentation of bacterial meningitis includes two or more of the following four symptoms and signs: 1) fever (greater than or equal to 38.5° C), 2) headache, 3) stiff neck, and 4) an altered level of consciousness.[1] A symptom that is often present, but under recognized as a symptom of central nervous system (CNS) infection, is vomiting.

Encephalitis is an acute febrile illness that typically begins with headache, which is then followed by difficulty with memory, behavioral changes, an altered level of consciousness and focal or generalized seizures.

When bacterial meningitis or encephalitis is considered a possibility, obtain blood cultures and initiate empiric antimicrobial and adjunctive therapy.

Empiric antimicrobial therapy is based on predisposing and associated conditions which predict the meningeal pathogen. Almost all recommended empiric antimicrobial regimens include a third-or fourth generation cephalosporin plus vancomycin. Ampicillin is added for coverage of *Listeria monocytogenes* where indicated, and metronidazole when the predisposing conditions of otitis, sinusitis or mastoiditis are present.[2] Acyclovir is added to empiric therapy for HSV-1 encephalitis.

Both the Infectious Diseases Society of America Practice Guidelines for the Management of Bacterial Meningitis[3] and the European Federation of Neurological Societies Guideline on the Management of Community-Acquired Bacterial Meningitis[4] recommend the use of dexamethasone in adults with suspected or proven pneumococcal meningitis. The Infectious Diseases Society of America Practice Guidelines also acknowledged that “some authorities would initiate dexamethasone in all adults with suspected bacterial meningitis because the etiology of meningitis is not always ascertained at initial evaluation.”[3] Heckenberg et al. demonstrated reduced rates of death and hearing loss and no evidence that dexamethasone was harmful in patients with meningococcal meningitis.[5]

Experimental models demonstrate efficacy for dexamethasone in herpes simplex virus encephalitis.[6]

The greatest mimic for bacterial meningitis is medication-induced meningitis, which may have a similar clinical presentation and spinal fluid formula as bacterial meningitis. The clinical presentation includes fever, headache, stiff neck, lethargy, confusion, seizures and coma. Spinal fluid analysis may demonstrate an increased opening pressure, a pleocytosis of polymorphonuclear leukocytes and a decreased glucose concentration. There may be diffuse enhancement of the meninges post the administration of contrast on CT or MRI. Cerebrospinal fluid Gram’s stain and culture are negative, and the symptoms resolve promptly when the offending medication is discontinued.[7]

Viral meningitis

The enteroviruses are the most common causative agents of viral meningitis. There is no specific antiviral therapy for meningitis due to an enterovirus, but patients get symptomatically better with nonsteroidal anti-inflammatory agents and amitriptyline. Herpes simplex virus-2 can cause meningitis at the time of the primary episode of genital herpes and is often the etiological agent of recurrent lymphocytic meningitis (Mollaret’s meningitis). The decision to treat HSV-2 meningitis with an antiviral agent (valacyclovir 1000 mg tid, famciclovir 500 mg tid or acyclovir 800 mg five times daily) for 7-14 days is based on best clinical judgement. Antiviral therapy shortens the duration of viral shedding. The authors of a retrospective observational study concluded that immunocompromised patients (HIV, diabetes mellitus) with HSV meningitis be treated with a 7-10 day course of antiviral therapy based on twelve patients that were treated with diverse oral, subq and intravenous antiviral therapies.[8]

Should temporal arteritis be treated with acyclovir? When should acyclovir be added to the therapy of ischemic stroke?

Dr. Gilden et al., detected VZV antigen in 61/82 (74%) giant cell arteritis-positive temporal artery biopsies compared with 1/13 (8%) normal temporal arteries and recommended that antiviral treatment may be beneficial in patients treated with corticosteroids. [9] Varicella zoster virus is the only human virus that has been shown to replicate in arteries and produce disease. Varicella zoster virus may cause ischemic stroke and cerebral aneurysms.[10]

Lyme disease

Neurologic Lyme disease may manifest as a seventh nerve or bilateral seventh nerve palsies (cranial nerves III, IV and VI may also be involved), a radiculitis, a mononeuritis multiplex and/or a lymphocytic meningitis. Look for the lesion of erythema migrans and send serology for the enzyme-linked immunosorbent assay (ELISA). When positive, the Western Blot (separate IgM and IgG immunoblots) is performed by a laboratory that is following the recommended protocol. The trouble maker is the false positive IgM. Avoid using the "Lyme labs."

Spinal fluid analysis demonstrates a lymphocytic pleocytosis, a mildly increased protein concentration and a normal glucose concentration.

In the United States, the demonstration of anti-Borrelia burgdorferi antibodies in CSF had previously been regarded as definitive evidence of neurologic Lyme disease based on the assumption that the presence of antibodies in CSF is evidence of intrathecal antibody production. This is incorrect.

The determination of the intrathecal production of antibodies to an organism requires more than the detection of antibodies in CSF, as antibodies can be passively transferred from serum to CSF, and Lyme antibodies may persist in the CSF for years. An antibody index is recommended to detect the intrathecal production of antibodies. The antibody index is the ratio of (anti-Borrelia IgG in CSF/anti-Borrelia IgG in serum) to (total IgG in CSF/total IgG in serum). The antibody index is, in general, considered positive when the result is >1.3 to 1.5. The anti-Borrelia antibody index can be used to determine if a seropositive patient with nonspecific symptoms in whom the clinical suspicion of neurologic Lyme disease is low, needs to be treated.

Neurologic Lyme disease is treated with doxycycline 100 mg twice daily for 14 days.[11] Doxycycline is contraindicated during pregnancy or lactation and for children younger than 8 years of age. Patients who are acutely ill or not improving on oral therapy can be treated with intravenous ceftriaxone (2 grams once daily), intravenous penicillin G (18–24 million units daily in divided doses every 4 hr) or intravenous cefotaxime (2 grams every 8 hr) for 14 days. According to European studies, doxycycline 100 mg po twice daily to four times daily for three to four weeks is also efficacious for meningitis. Patients remain seropositive for years post-treatment and anti-B. burgdorferi antibodies may persist in CSF.

Chronic Lyme disease

Chronic Lyme disease is a diagnosis fueled by patients and practitioners to explain prolonged complaints of fatigue, cognitive dysfunction and pain. Support for "chronic Lyme disease" comes from the "Lyme labs" overinterpretation of weak IgM bands, and the belief that morphologic variants of *Borrelia burgdorferi* ('cyst forms', 'cell-wall deficient forms', 'unstable L-forms" etc.) are responsible for "chronic Lyme disease."[12] There is a high frequency of false positive Lyme disease IgM Western blots.[13]

"Posttreatment Lyme disease syndrome is not due to ongoing CNS infection or inflammation and should not be considered a neurologic disorder at all."[14]

Elderly demented patient with positive RPR

The initial step in diagnosis and management is to obtain a treponemal test.

Treponemal tests (detect specific antibodies against *Treponema pallidum)*:

FTA-ABS (Fluorescent treponemal antibody-absorbed test).

TPPA (*Treponema pallidum* particle agglutination test).

Nontreponemal tests (detect antibodies to lipids found on the membranes of *T. pallidum)*:

RPR
VDRL

If positive FTA-ABS or TPPA, then obtain spinal fluid.

Neurosyphilis:

Positive CSF VDRL - treat for neurosyphilis. Note: a false positive CSF VDRL may occur in a traumatic tap.

Negative CSF FTA-ABS, negative CSF VDRL, no pleocytosis, normal protein concentration– no treatment required.

Nonreactive CSF VDRL, increased white blood cell count and/or protein concentration – treat for neurosyphilis.

Treatment for neurosyphilis: aqueous crystalline penicillin G, 18-24 million units per day for 10-14 days.

Multiple enhancing lesions in an HIV-infected individual

The differential diagnosis is *Toxoplasma gondii* and CNS lymphoma and anti-Toxoplasma IgG should be obtained on serum. A single lesion favors lymphoma, multiple ring –enhancing lesions favor toxoplasmosis.

Empiric therapy for toxoplasmosis is initiated if the following criteria are met: 1) positive serology for anti-Toxoplasma IgG; 2) CD4 count less than 200 cells/mm^3; 3) multiple ring enhancing lesions on MRI: 4) not taking anti-toxoplasma antimicrobial therapy (TMP-SMX [trimethoprim-sulfamethoxazole] or pyrimethamine-sulfadoxine) prophylactically.

Empiric therapy is a combination of pyrimethamine, sulfadiazine and folinic acid. The expected clinical response is a 50% improvement in the patient's clinical examination by day 7 of treatment.[15]

Is the lesion in my patient a lesion of neurocysticercosis, and what do I do about it?

Cysticercal cysts evolve through four stages, with different appearances on neuroimaging:

1) the vesicular stage, where the cyst contains a living larva (scolex seen on CT and MRI);
2) a colloidal stage as the larva degenerates (edema surrounds lesion);
3) a "granulo-nodular" stage as the membrane of the cyst thickens;
4) the final stage of calcification.[16]

Only cysts in the vesicular and colloidal stages contain live larvae and are amenable to anticysticercal treatment.

Have ophthalmology perform an examination for subretinal parasites.
Send stool for ova and parasites in patient and all household members, or alternatively, treat everyone.
Can send serum for enzyme-linked immunoelectrotransfer blot assay.

Treatment of intraparenchymal neurocysticercosis: Albendazole (15 mg/kg per day bid for 7 days) plus prednisone.

The treatment of extraparenchymal neurocyticercosis is more complicated and requires neurosurgical procedures and antiparasitic treatment.[17-18]

Zika virus and Guillian-Barre syndrome

There is a serum RT-PCR but viral nucleic acid is often only found in the first week of viremia, CSF IgM (send CSF IgM for dengue as well), and send acute and convalescent sera (four weeks apart) for Zika virus IgG looking for a fourfold increase in IgG. The best body fluid for Zika virus RNA is semen.[19]

References

1. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med 2004;351: 1849-59.
2. Roos KL, van de Beek D. Bacterial meningitis. In: Roos KR, Tunkel AR, editors. Handbook of Clinical Neurology. Edinburgh: Elsevier; 2010. p 51-63.
3. Tunkel AR, Hartman BJ, Kaplan BA, et al. Practice Guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267-1284.
4. Chaudhuri A, Martin PM, Kennedy PGE, Seaton A, et al. EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. Eur J Neurol 2008:15: 649-659.
5. Heckenberg SGB, Brouwer MC, van der Ende A, van de Beek D. Adjunctive dexamethasone in adults with bacterial meningitis. Neurology 2012;79:1563-1569.
6. Ramos-Estebanez C, Lizarraga KJ, Merendo A. A systematic review on the role of adjunctive corticosteroids in herpes simplex virus encephalitis: is timing critical for safety and efficacy. Antiviral Therapy 2014;19:133-139.
7. De Marcaida JA, Reik L. Disorders that mimic central nervous system infections. In: Marra CM, ed. Neurologic Clinics;17(4):1999, pgs. 901-941.
8. Noska A, Kyrillos R, Hansen G, Hirigoyen D, Williams DN. The role of antiviral therapy in immunocompromised patients with herpes simplex virus meningitis. Clin Infect Dis 2015;60(2):237-42.
9. Gilden D, et al. Prevalence and distribution of VZV in temporal arteries of patients with giant cell arteritis. Neurology 2015;84:1948-1955.
10. Nagel MA, Gilden D. Developments in varicella zoster vasculopathy. Curr Neurol Neurosci Rep 2016;16:12
11. Halperin JJ, Shapiro ED, Logigian EL, et al. Practice parameter: treatment of nervous system Lyme disease. Neurology. 2007;69 (1):91-102.
12. Lantos PM, Auwaerter PG, Wormser GP. A systematic review of *Borrelia burgdorferi* morphologic variants does not support a role in chronic Lyme disease. Clin Infect Dis 2014;58(5):663-71.
13. Lantos PM, Branda JA, Boggan JC, et al. Poor positive predictive value of Lyme disease serologic testing in an area of low disease incidence. Clin Infect Dis 2015;61:1374-80.
14. Halperin JJ. Neuroborreliosis: what is it, what isn't it? Clin Infect Dis 2016;63(3):354-5.
15. Montoya JG. *Toxoplasma gondii* and toxoplasmosis. In : In: Scheld WM, Whitley RJ, Marra CM, eds. Infections of the Central Nervous System, 4rd ed. Philadelphia: Wolters Kluwer Health;2014;745-755.
16. Baird A, Wiebe S, Zunt J, Halperin JJ, Gronseth G, Roos KL. Evidence-based guideline: Treatment of parenchymal neurocysticercosis. Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2013;80:1424-1429.
17. Garcia HH, Nash TE, Del Brutto OH. Clinical symptoms, diagnosis, and treatment of neurocysticercosis. Lancet Neurol 2014;13:1202-15.
18. Del Brutto OH. Clinical Management of neurocysticercosis. Expert Rev Neurother 2014;14:389-396.
19. PetersenLR, Jamieson DJ, Powers AM, Honein MA. Zika virus. N Engl J Med 2016;374:1552-63.